

Role for lower extremity interstitial fluid volume changes in the development of orthostasis after simulated microgravity.

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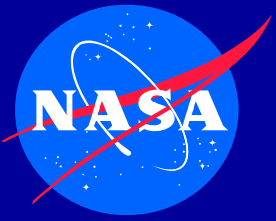
Abstract

Introduction: Reentry orthostasis after exposure to the conditions of spaceflight is a persistent problem among astronauts. In a previous study, a computer model systems analysis was used to examine the physiologic mechanisms involved in this phenomenon. In this analysis, it was determined that an augmented capacitance of lower extremity veins due to a fluid volume contracture of the surrounding interstitial spaces during spaceflight results in an increase in sequestered blood volume upon standing and appears to be the initiating mechanism responsible for reentry orthostasis. In this study, we attempt to validate the central premise of this hypothesis using a ground-based spaceflight analog.

Methods: 10 healthy subjects were placed at bed rest in a 6° head down tilt position for 60 days of bed rest. The impact of adaptations in interstitial fluid volume and venous capacitance in the lower extremities were then observed during a standard tilt test protocol performed before and after the confinement period. The interstitial thickness superficial to the calcaneus immediately below the lateral malleolus was measured using ultrasound with a 17-5 MHz linear array transducer. Measurements of the changes in anterior tibial vein diameter during tilt were obtained by similar methods. The measurements were taken while the subjects were supine and then during upright tilt (80°) for thirty minutes, or until the subject had signs of presyncope. Additional measurements of the superficial left tibia interstitial thickness and stroke volume by standard echocardiographic methods were also recorded. In addition, calf compliance was measured over a pressure range of 10-60 mmHg, using plethysmography, in a subset of these subjects (n = 5).

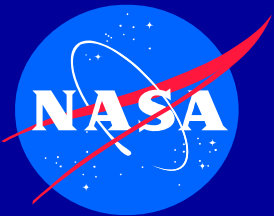
Results: There was an average of 6 % diminution in the size of the lower extremity interstitial space as compared to measurements acquired prior to bed rest. This contracture of the interstitial space coincided with a subsequent relative increase in the percentage change in tibial vein diameter and stroke volume upon tilting in contrast to the observations made before bed rest (54 vs 23% respectively). Compliance in the calf increased by an average of 36% by day 27 of bedrest.

Conclusions: A systems analysis using a computer model of cardiovascular physiology suggests that microgravity induced interstitial volume depletion results in an accentuation of venous blood volume sequestration and is the initiating event in reentry orthostasis. This hypothesis was tested in volunteer subjects using a ground-based spaceflight analog model that simulated the body fluid redistribution induced by microgravity exposure. Measurements of changes in the interstitial spaces and observed responses of the anterior tibial vein with tilt, together with the increase in calf compliance, were consistent with our proposed mechanism for the initiation of postflight orthostasis often seen in astronauts.



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Introduction

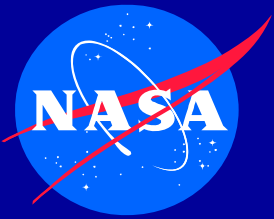
Orthostatic intolerance after exposure to the conditions of spaceflight continues to be a problem among astronauts

20-30% of returning short-duration crew members experience hypotension that progresses to presyncope during a 10 minute tilt test, while 83% of long-duration crew experience presyncope

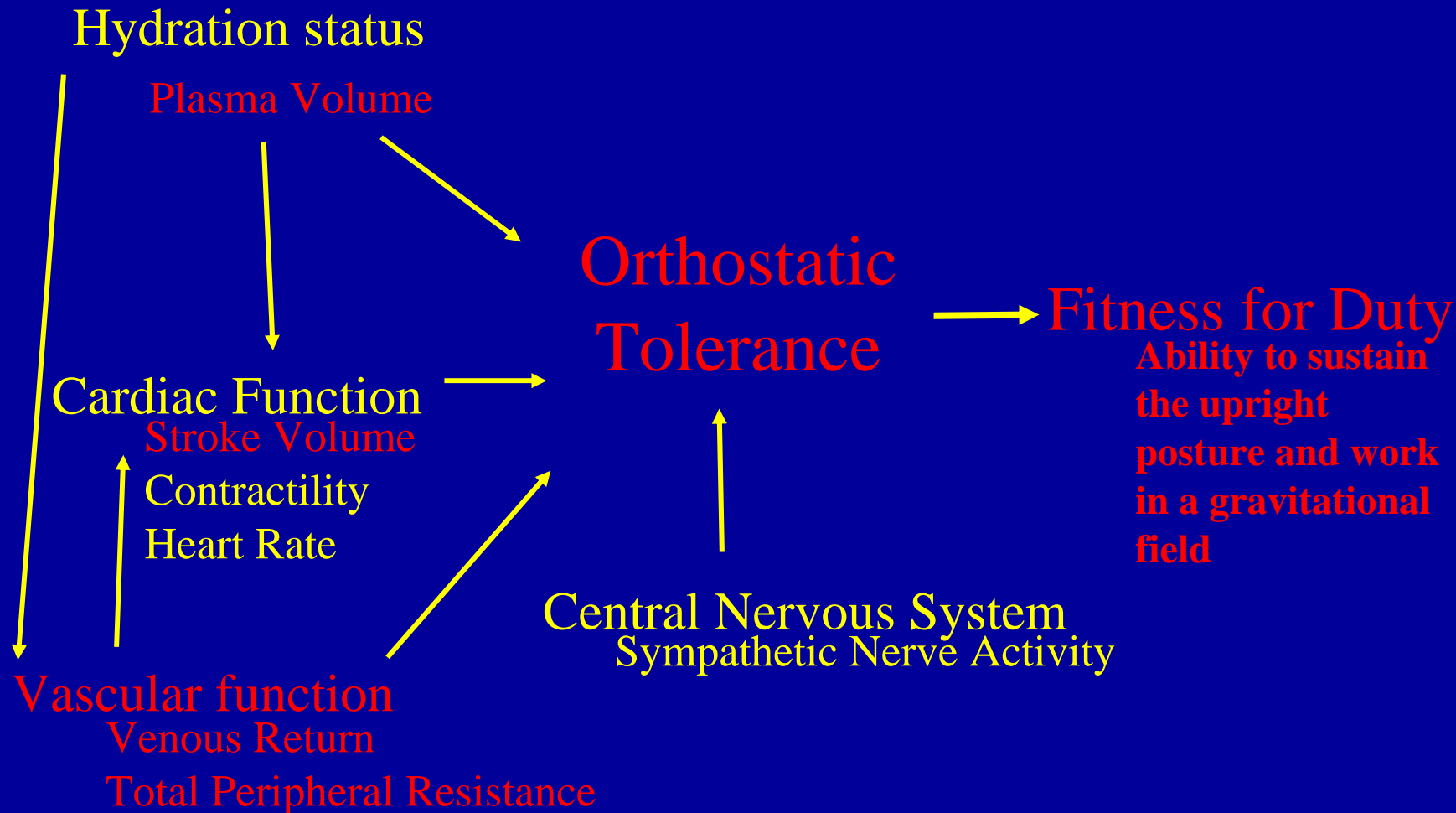
Several mechanisms have been proposed to account for this phenomenon including altered; cardiac function, vascular function and adrenergic control.

In a previous study, a computer model systems analysis was used to examine the physiologic mechanisms involved in orthostatic intolerance. In this analysis, it was determined that an augmented capacitance of lower extremity veins due to a fluid volume contracture of the surrounding interstitial spaces during spaceflight results in an increase in sequestered blood volume upon standing and appears to be an initiating mechanism responsible for reentry orthostasis.

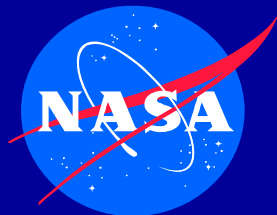
In this study, we attempt to validate the central premise of this hypothesis using 60 days of head down tilt bed rest as a ground-based spaceflight analog.



Orthostatic Tolerance in Context







Spaceflight-induced plasma volume changes

	Day of Testing	Presyncopal on Landing Day			Nonpresyncopal on Landing Day		
		Supine	Upright	Upright-supine	Supine	Upright	Upright-supine
Hematocrit, %	Preflight	39 ± 1 (8)	42 ± 2 ^a (8)	2.8 ± 0.6 (8)	40 ± 1 (13)	44 ± 1 ^a (13)	3.3 ± 0.4 (13)
	Landing day	39 ± 1 ^b (8)	42 ± 1 ^a (8)	3.1 ± 0.7 (8)	42 ± 1 (13)	44 ± 1 ^a (12)	2.8 ± 0.9 (12)
	3 Days after landing	38 ± 1 (8)	40 ± 1 ^{a,d} (8)	2.2 ± 0.6 (8)	38 ± 1 ^{c,d} (13)	41 ± 1 ^{a,c,d} (13)	2.6 ± 0.4 (13)
Plasma volume, l/m ²	Preflight	1.83 ± 0.11 (8)			1.84 ± 0.07 (9)		
	Landing day	1.70 ± 0.09 ^e (8)			1.65 ± 0.08 ^e (9)		
	3 Days after landing	1.91 ± 0.12 ^d (8)			1.92 ± 0.12 ^d (9)		

Meck et al, 2004

Table 1. Supine Measurements of Plasma Volume (l/m²)

	Preflight	Landing day	Three Days Postflight	% Spaceflight-Induced Loss
Presyncopal Women (n=5)	1.81 ± 0.17	1.44 ± 0.08 ^{*‡}	2.02 ± 0.11 (n=4)	19.5 ± 0.04 [§]
Presyncopal Men (n=6)	1.67 ± 0.12	1.55 ± 0.12 [*]	1.66 ± 0.12	7.1 ± 0.03
Non-Presyncopal Men (n=24)	1.73 ± 0.04	1.60 ± 0.05 ^{**‡}	1.81 ± 0.05	7.1 ± 0.03

Values are means ± SE; n, No. of subjects. ^{*}p ≤ 0.05, ^{**}p ≤ 0.01, vs. preflight [‡]p ≤ 0.01, vs. three days postflight. [§]p < 0.05 vs. presyncopal men and non-presyncopal men.

Waters et al, 2002

Where does the plasma volume go?

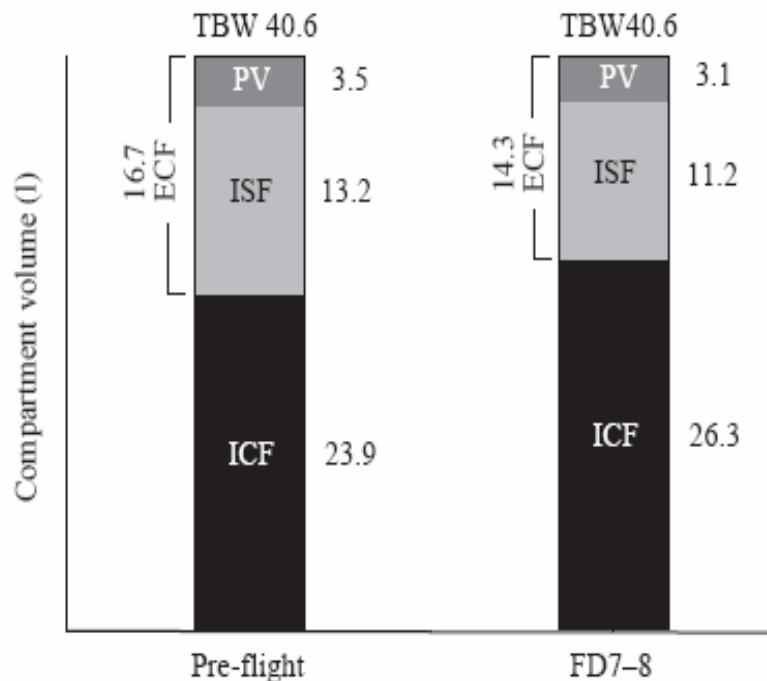


Fig. 3. Mean fluid compartment volumes before and during space flight. Data from Leach and colleagues (Leach et al., 1996) ($N=6$). TBW, total body water; ECF, extracellular fluid; PV, plasma volume; ISF, interstitial fluid; ICF, intracellular fluid; FD7-8, flight days 7-8.

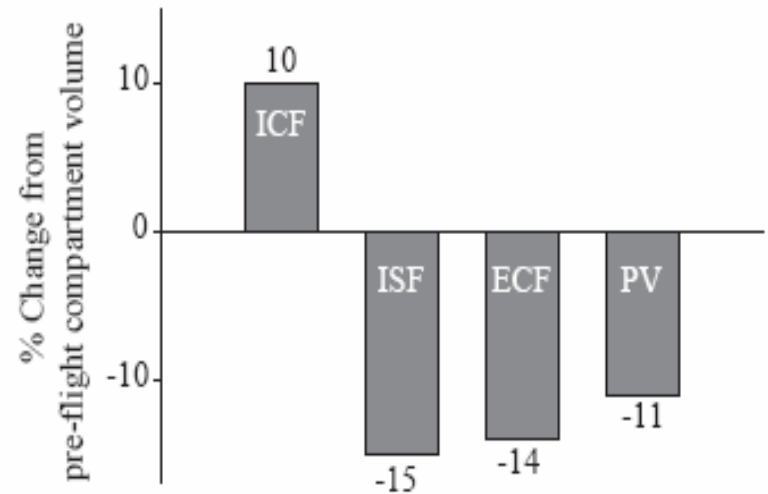
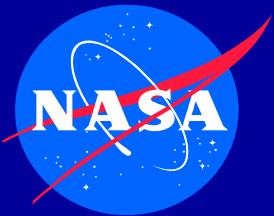


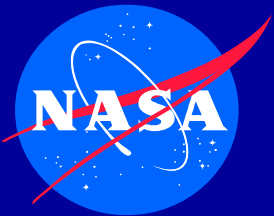
Fig. 4. Mean percentage change in fluid compartment volumes from pre-flight to flight days 7-8. Data from Leach and colleagues (Leach et al., 1996) ($N=6$). ICF, intracellular fluid; ISF, interstitial fluid; ECF, extracellular fluid; PV, plasma volume.



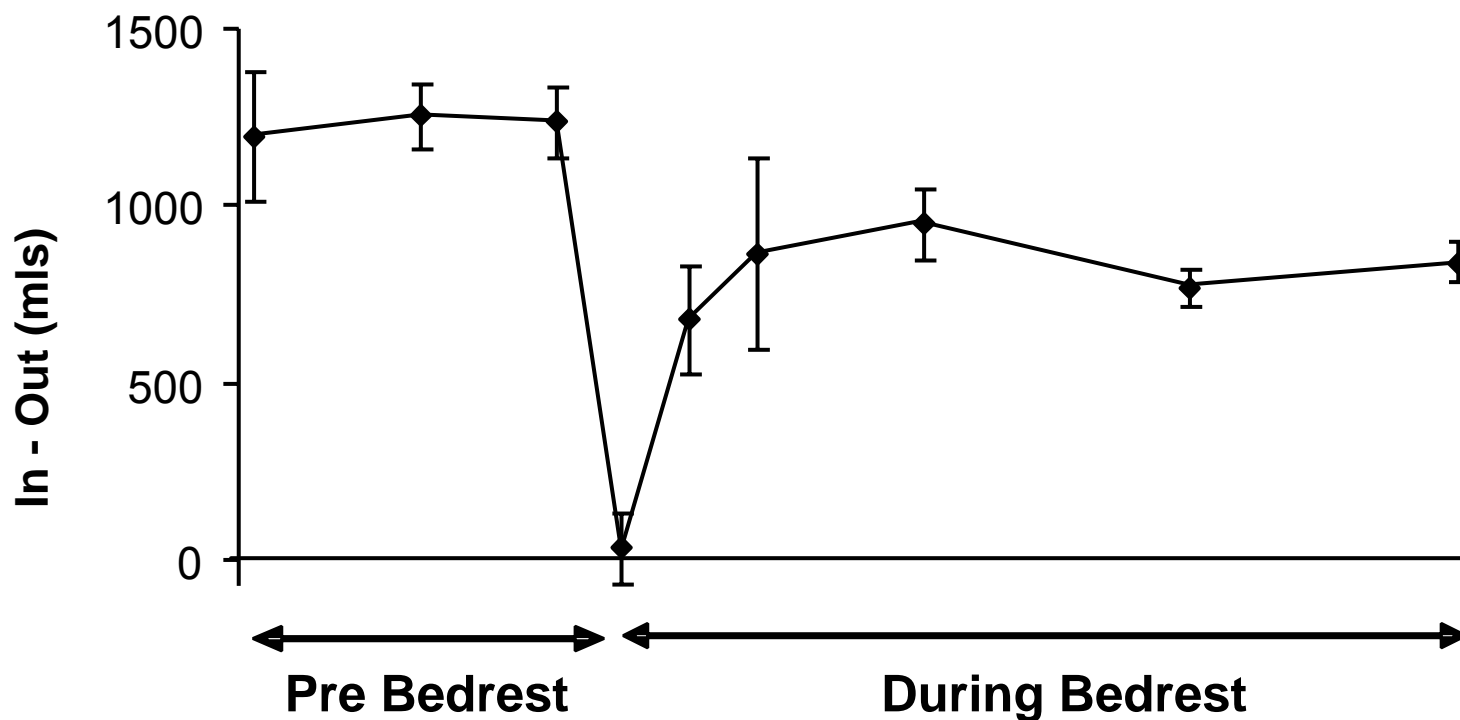
Plasma Volume Loss in Bed Rest

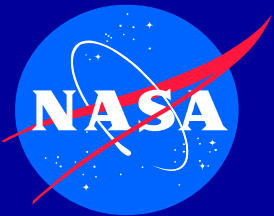
Table 4. *Effects of strict -6° head-down bed rest variables collected at rest and in response to orthostatic stress*

Study	Days of Strict -6° HDBR	<i>n</i>		Rate of Presyncope After Bed Rest	Volume Loss, %	HR	Stroke Volume	Peripheral Vascular Resistance	Venous Pressure	Muscle SNA	Plasma Norepinephrine	PRA or Active Renin
		Total	Men/women									
Beck et al. (2)	10	6	6/0	33%	16	$\leftrightarrow \uparrow$	$\downarrow \downarrow$	$\uparrow \uparrow$				
Convertino et al. (9)	30	11	11/0	40% ^a	15	$\uparrow \uparrow^d$					$\leftrightarrow \leftrightarrow$	
Convertino et al. (10)	7	11	11/0		13	$\uparrow \uparrow$	$\downarrow \downarrow$	\uparrow	$\downarrow \downarrow$		\downarrow	
Convertino et al. (12)	14	8	8/0		16	\uparrow		\uparrow			\downarrow	
Convertino et al. (11)	30	8	8/0		16	\uparrow					\downarrow	\uparrow
Crandall et al. (13)	15	7	7/0		16	\uparrow	\downarrow	\uparrow	\downarrow			
Goldstein et al. (18)	14	8	Not reported		16				\downarrow		\leftrightarrow	
Kamiya et al. (22)	14	20	20/0		12	\uparrow		\uparrow		\uparrow		
Kamiya et al. (23)	14	22	22/0	45%	13, 12 ^c	$\leftrightarrow \uparrow$			\downarrow	$\leftrightarrow \leftrightarrow \downarrow^f$		
Levine et al. (28)	14	12	11/1	\uparrow^b	17	\leftrightarrow	$\downarrow \downarrow$	\uparrow	\leftrightarrow			
Millet et al. (34)	7	8	0/8	71% ^a	9	$\leftrightarrow \leftrightarrow$					$\leftrightarrow \leftrightarrow$	$\uparrow \uparrow$
Millet et al. (34)	7	8	8/0	75%	9	$\leftrightarrow \leftrightarrow$					$\leftrightarrow \leftrightarrow$	$\uparrow \uparrow$
Shoemaker et al. (48)	14	15	15/0	40%		$\uparrow \leftrightarrow \uparrow$	$\leftrightarrow \leftrightarrow$	$\leftrightarrow \leftrightarrow$		$\leftrightarrow \uparrow^g \leftrightarrow \downarrow^f$		
Siguado et al. (49)	42	8	8/0	57% ^a	12	\uparrow					$\leftrightarrow \uparrow^g$	\uparrow
Vernikos et al. (54)	7	8	0/8		8	\uparrow						$\uparrow \uparrow$
Vernikos et al. (54)	7	8	8/0		4	\uparrow						$\leftrightarrow \uparrow$

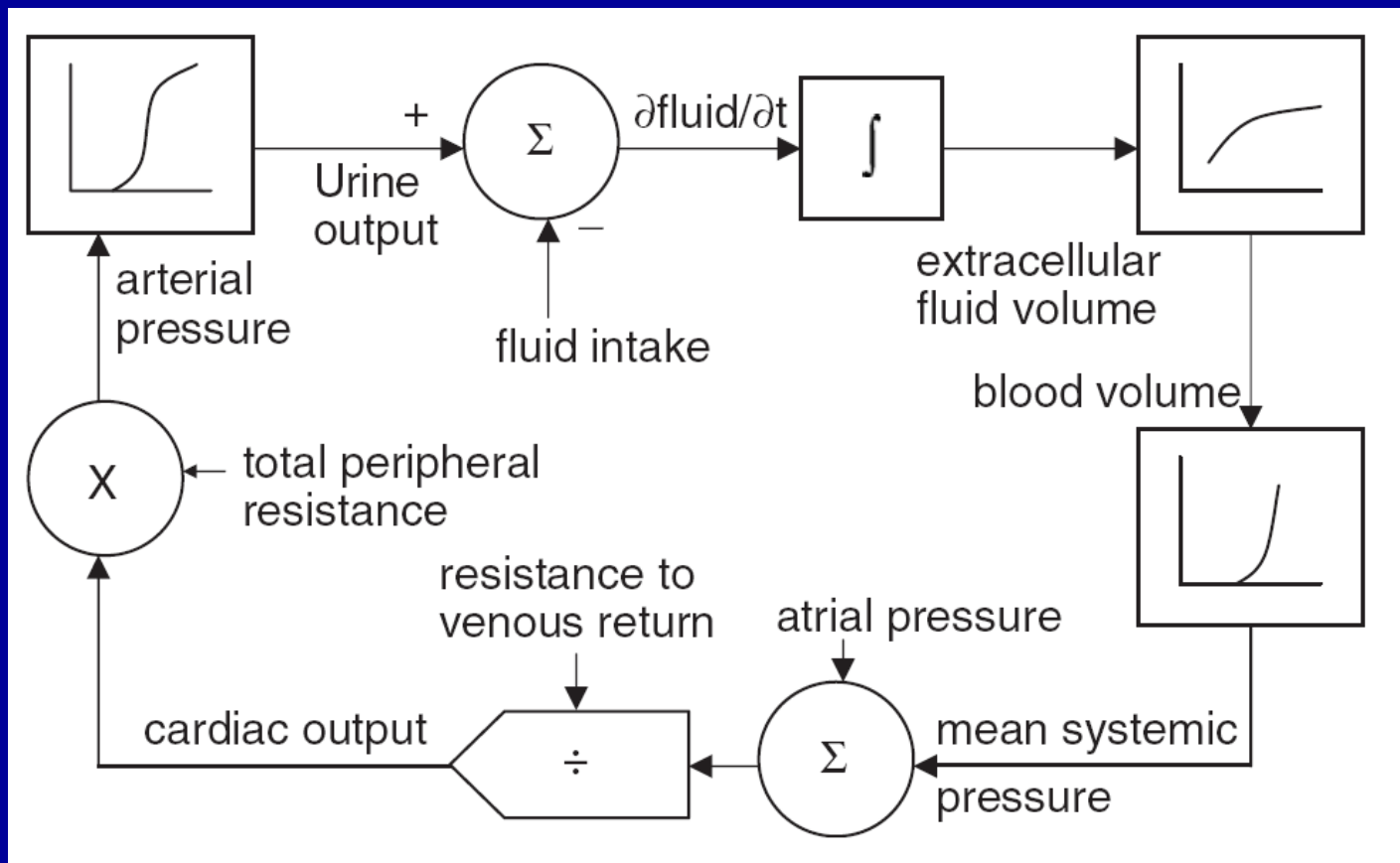


Fluid Intake Minus Urine Output in Bed Rest

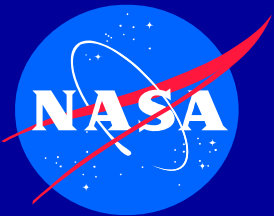




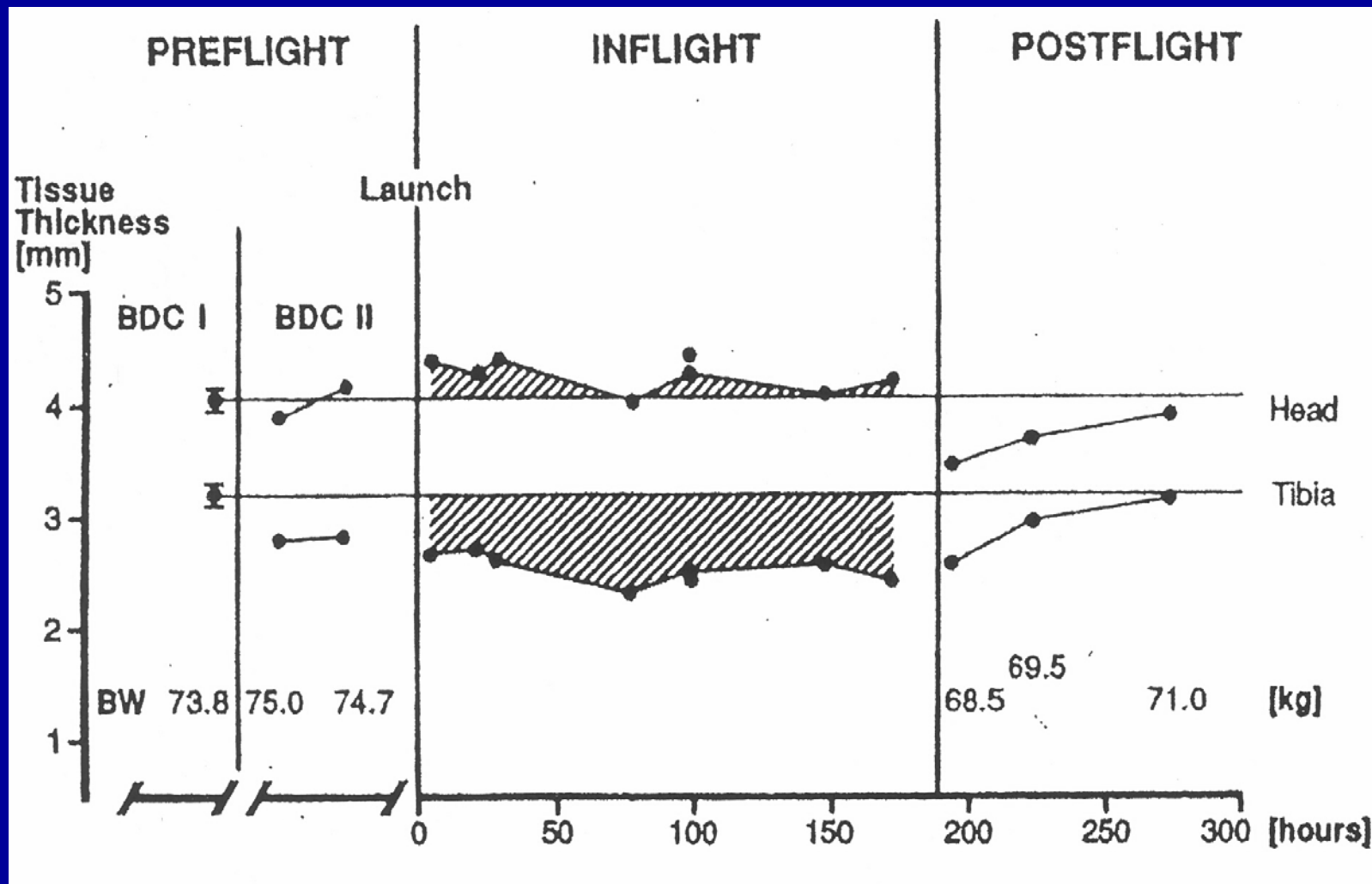
Body fluid feedback loop



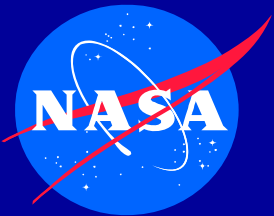
Current computerized model contains over 4,000 equations relating to human physiological responses



Interstitial Thickness in Space



From: Kirsch, KA. et al, 1993



Methods

17 healthy subjects (9 men, 8 women) were placed at strict bed rest in a 6° head down tilt position for 60 days (one subject for 54 days).

The interstitial thickness superficial to the calcaneus, immediately below the lateral malleolus, was measured using ultrasound with a 17-5 MHz linear array transducer before bedrest and following 60 days of bedrest. Forehead interstitial thickness was measured one inch cephalad from the eyebrows with the transducer perpendicular to the bone and centered on the forehead .

Measurements of the changes in anterior tibial vein area and anterior tibial artery diameter during tilt were obtained by similar methods.

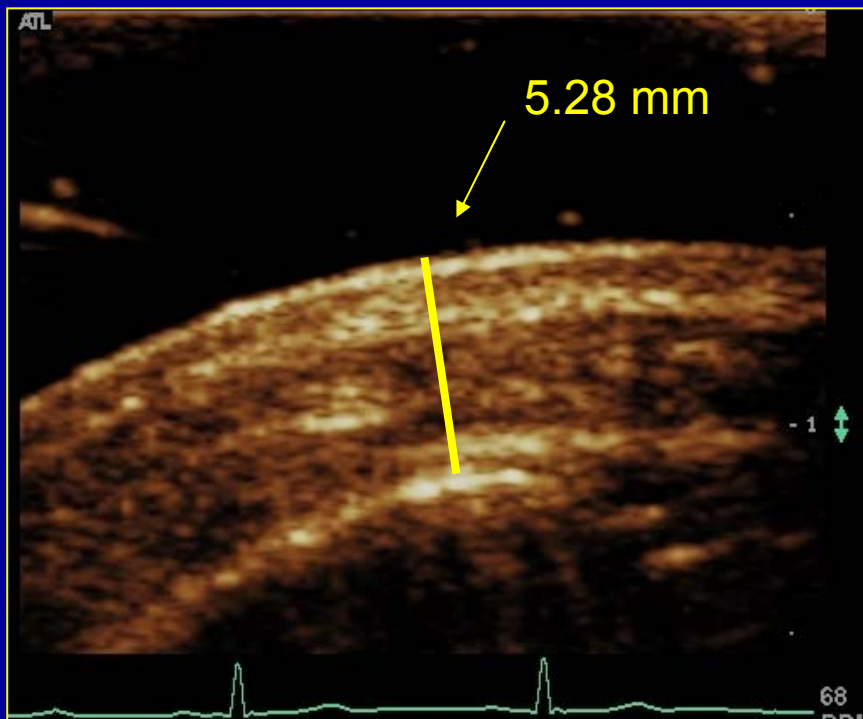
The measurements were taken while the subjects were supine and then for the first six minutes of upright tilt (80°).

Additional measurements included stroke volume (pulsed wave doppler), blood pressure (dynamap and finapres) and heart rate (ECG).

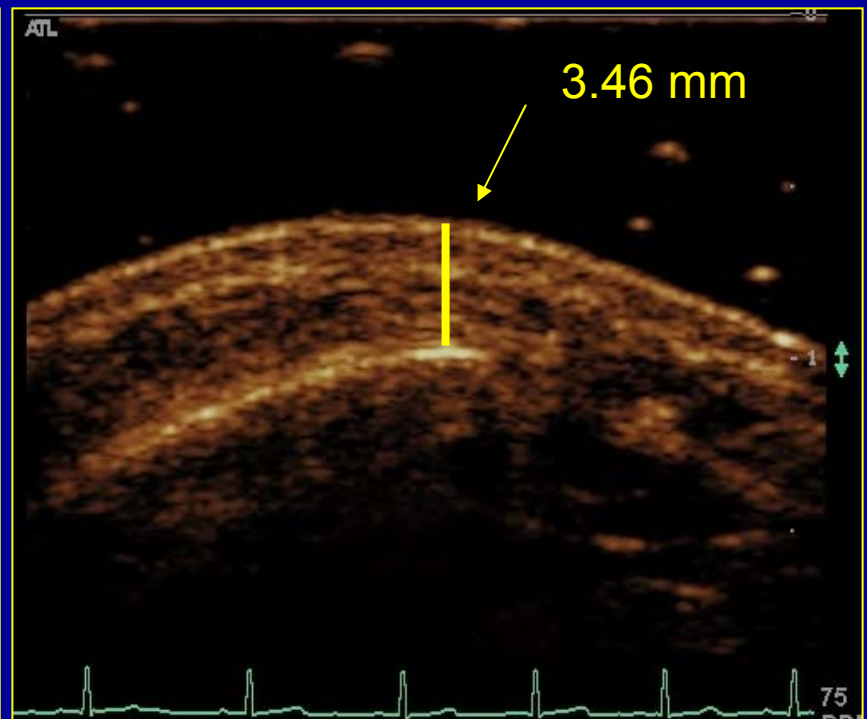


Pre-Tibial Supine Interstitial Thickness

Pre-Bed Rest



Bed Rest Day 60



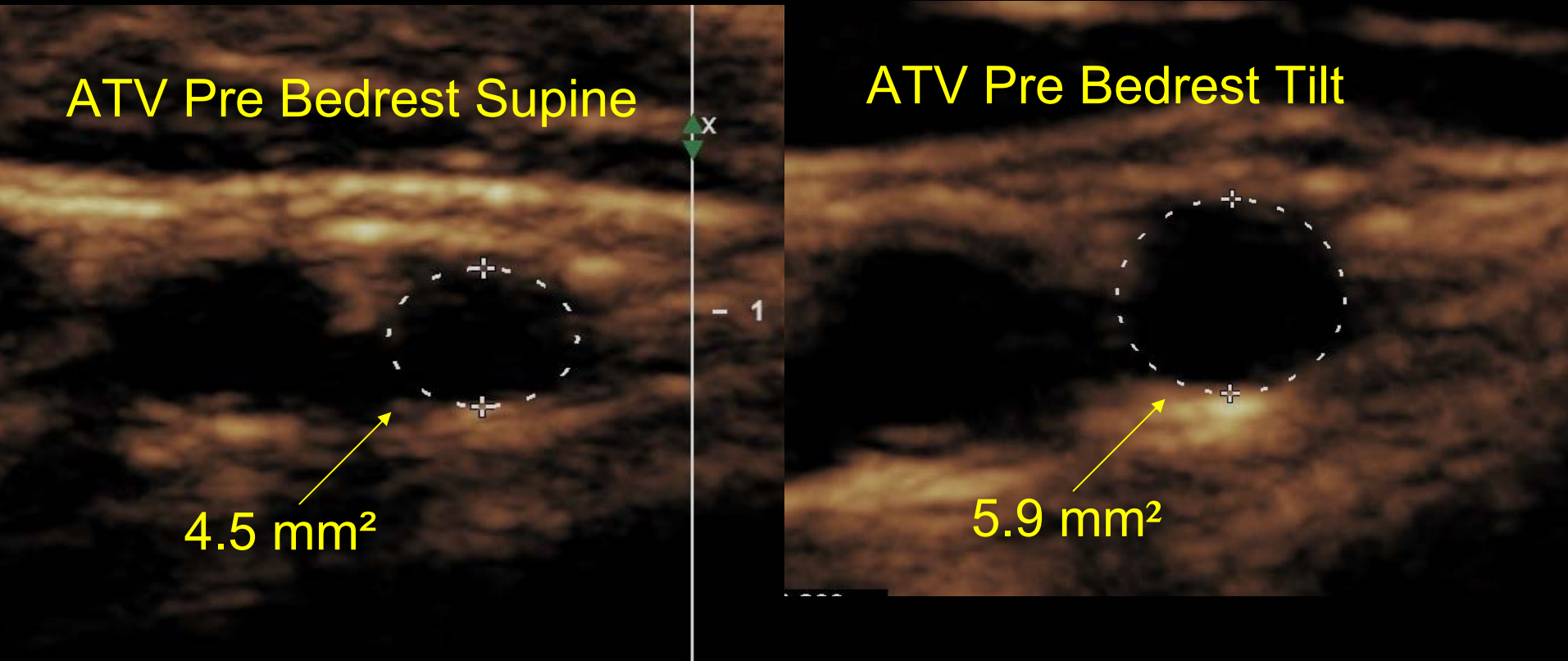
Anterior Tibial Vein Area

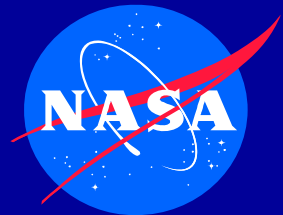
ATV Pre Bedrest Supine

4.5 mm²

ATV Pre Bedrest Tilt

5.9 mm²





Results

Age 32.76 ± 1.82 years

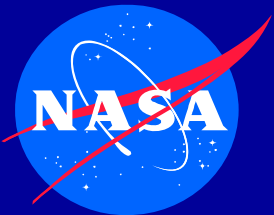
Height 169 ± 2.25 cm

Weight pre 71.93 ± 3.57

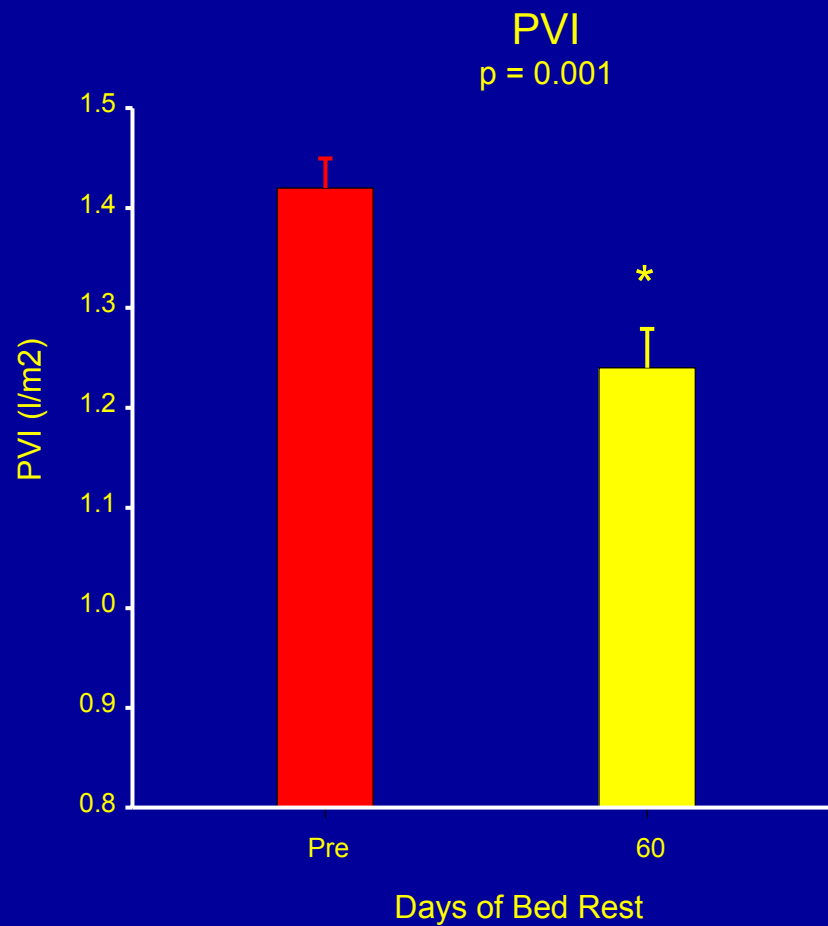
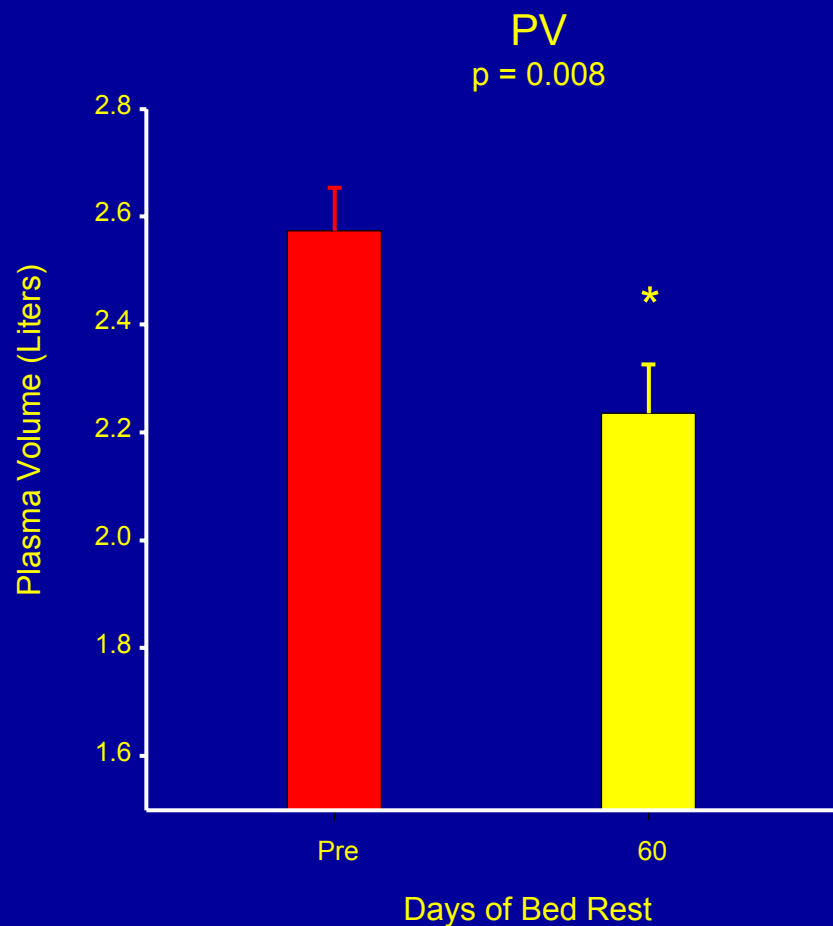
Day 60 70.76 ± 3.50

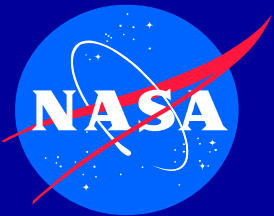
BMI pre 25.0 ± 0.91

Day 60 24.6 ± 0.88

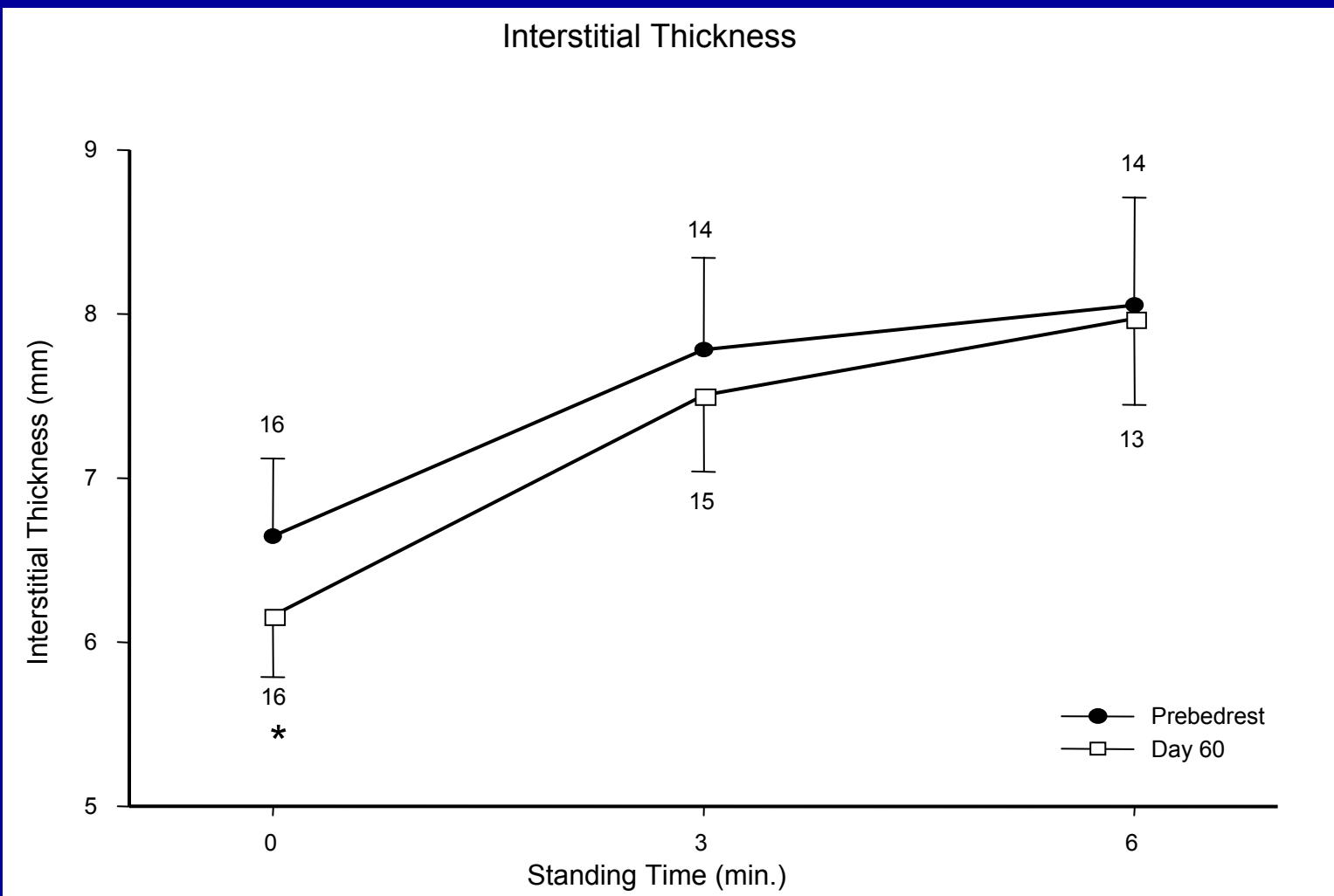


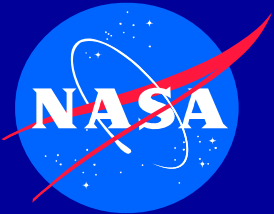
Effects of 60 Days Bed Rest on Plasma Volume



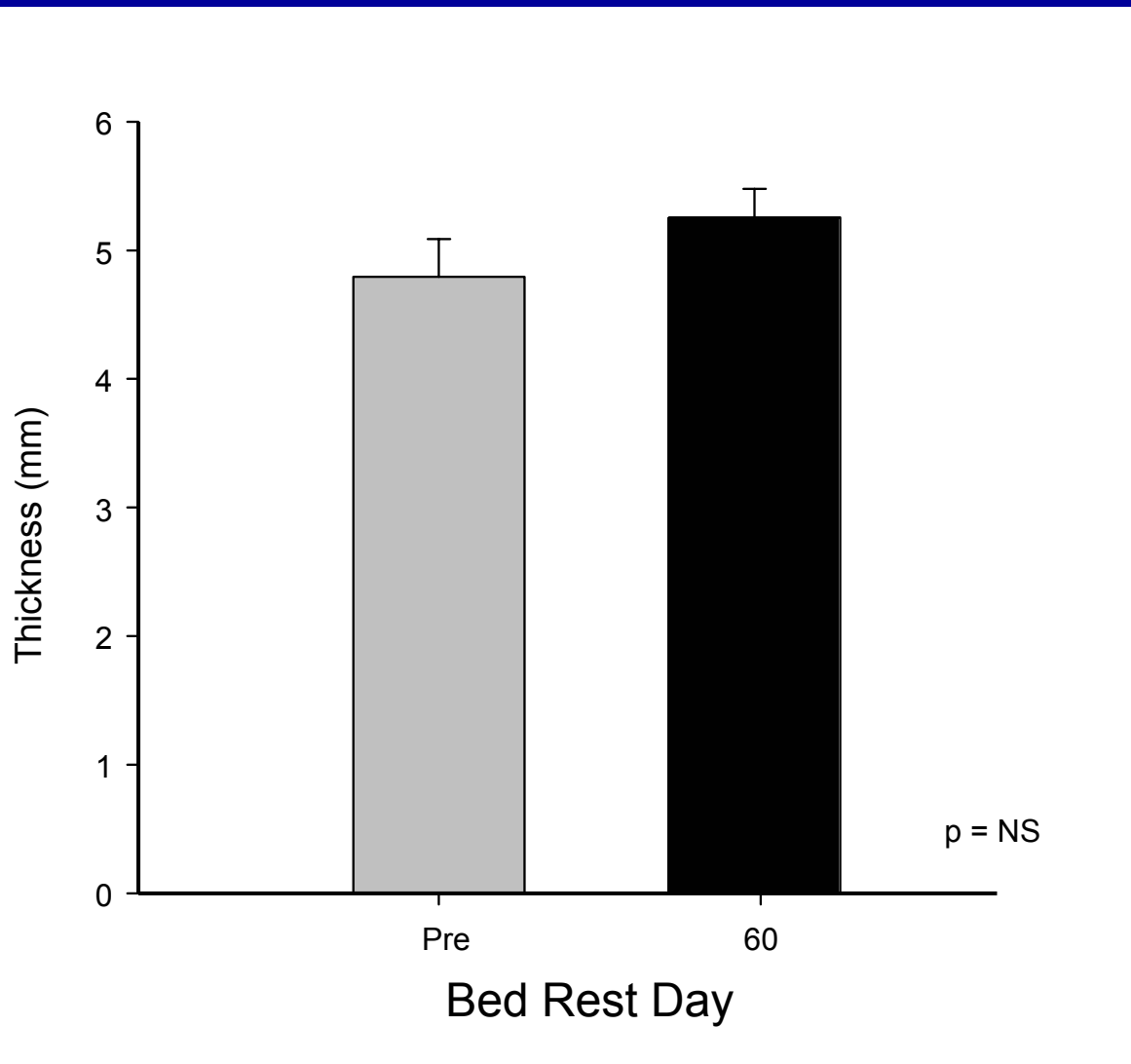


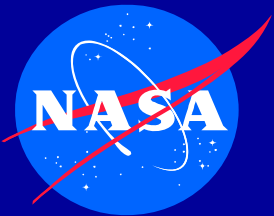
Effects of 60 Days Bed Rest Leg Interstitial Thickness



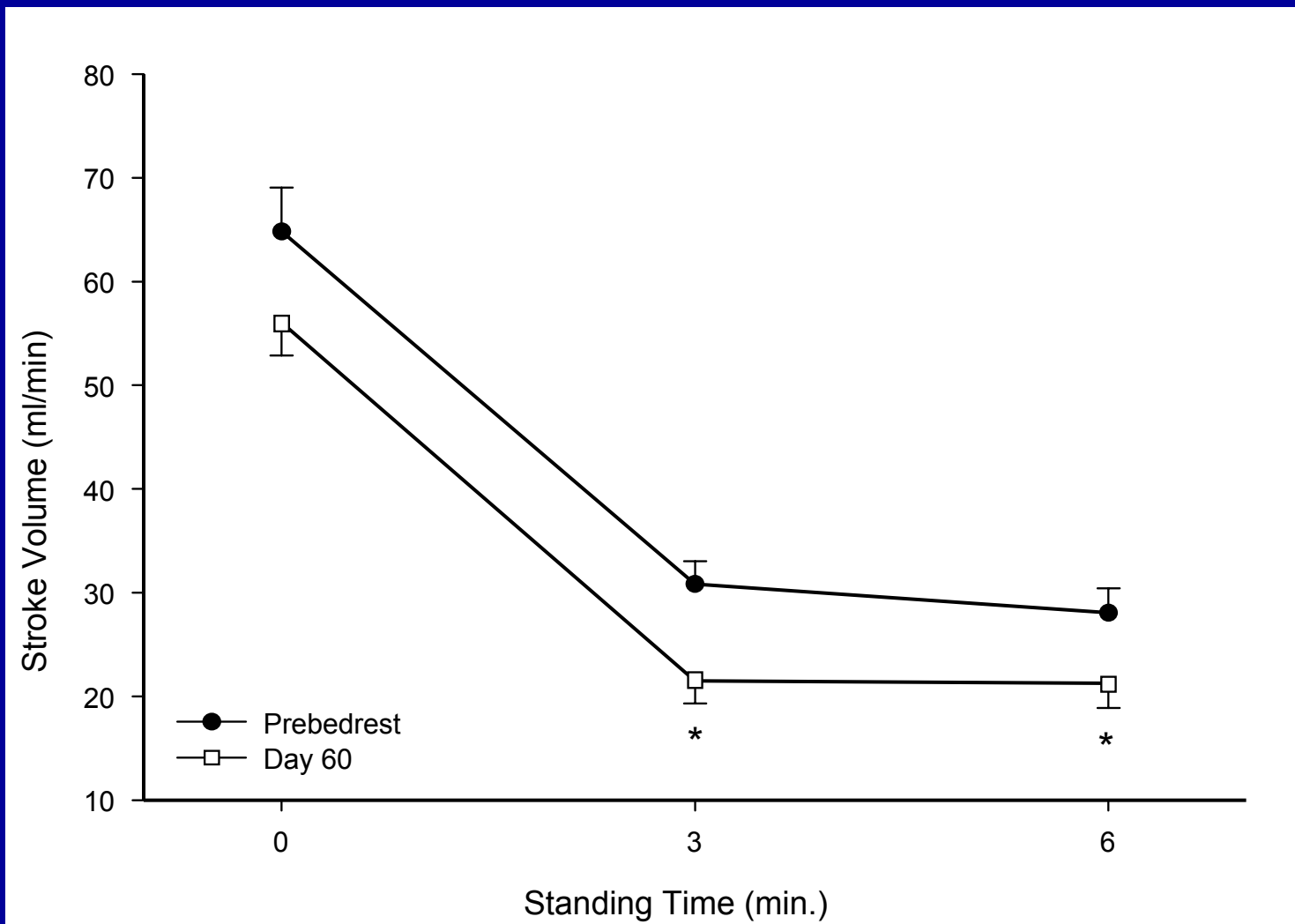


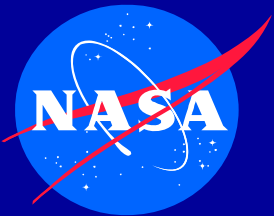
Effect of bed rest on supine forehead interstitial thickness



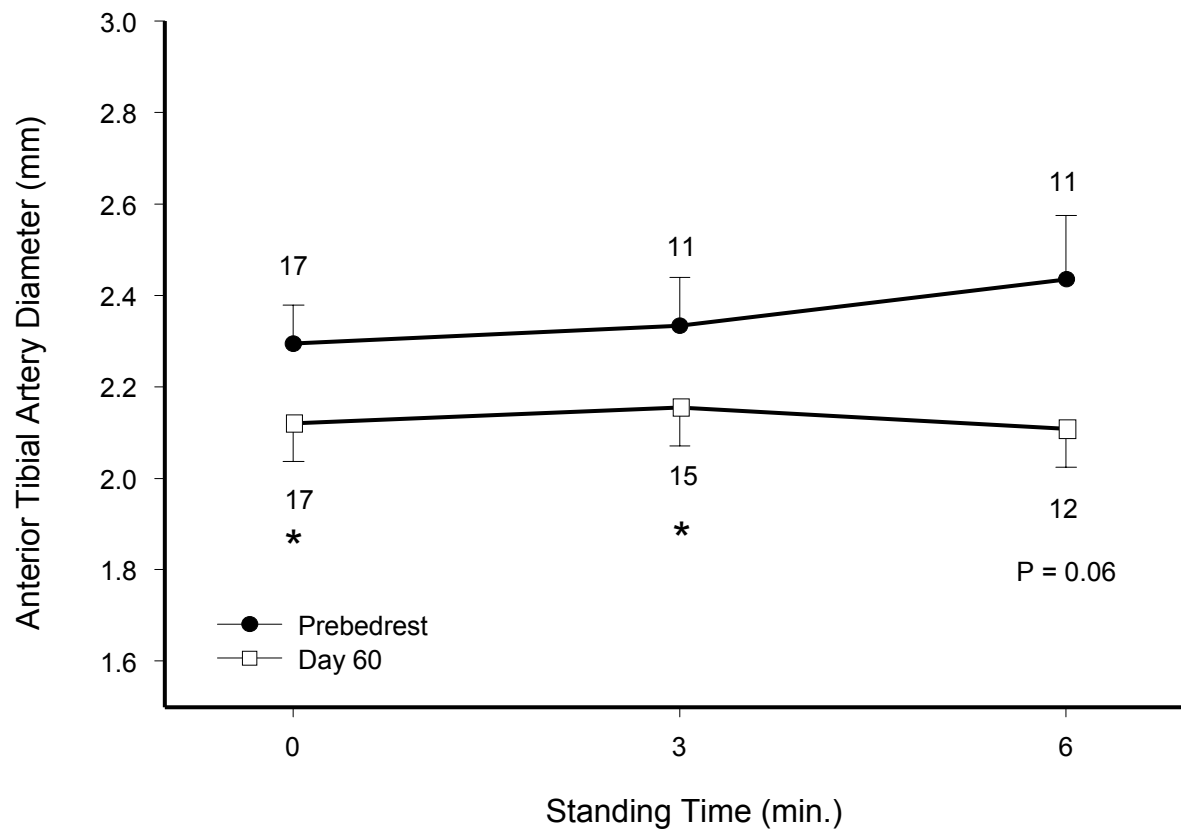


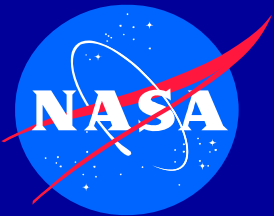
Effects of 60 Days Bed Rest on Stroke Volume



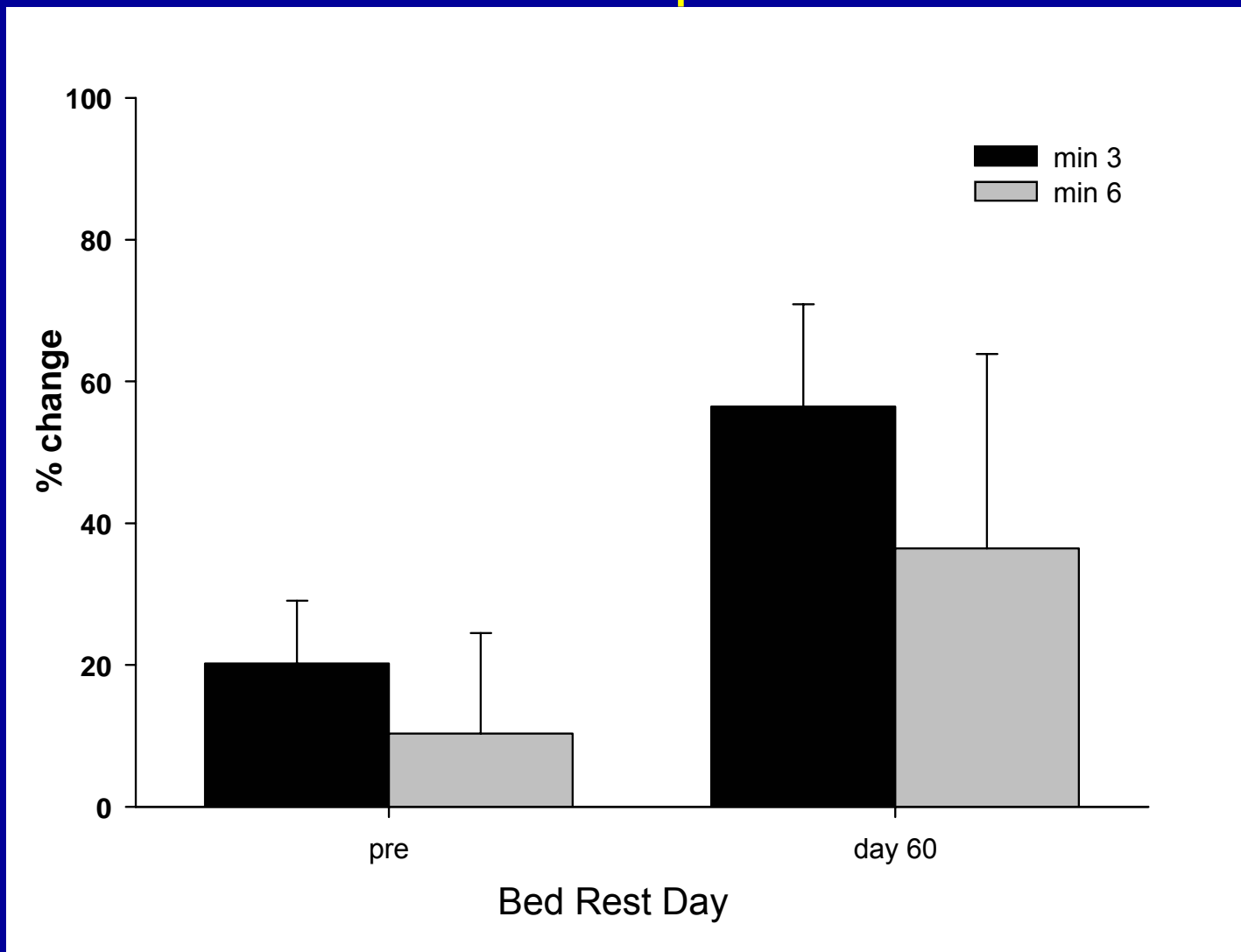


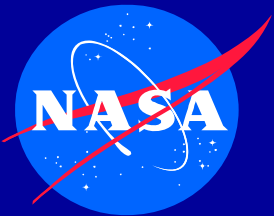
Effects of 60 Days Bed Rest on Anterior Tibial Artery Diameter





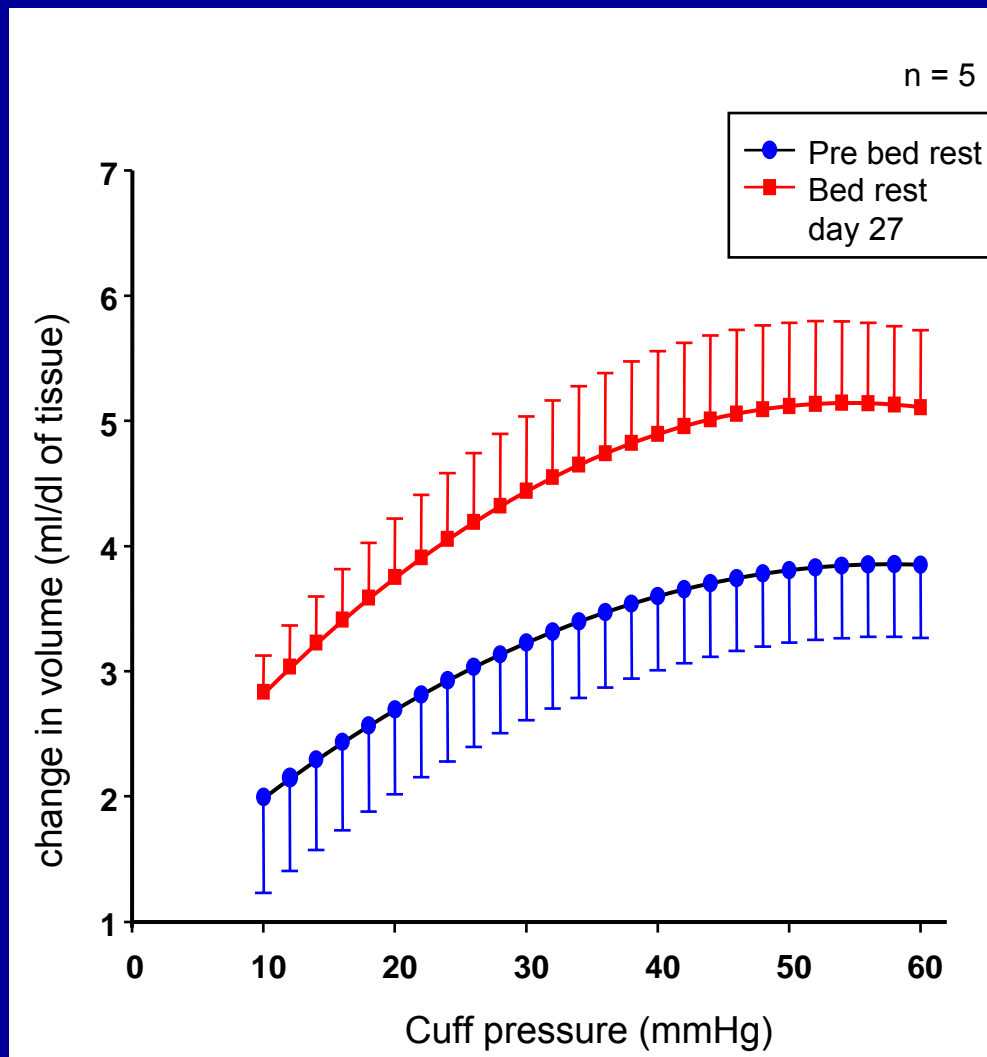
Effects of 60 Days Bed Rest on Anterior Tibial Vein Area: percent change from supine



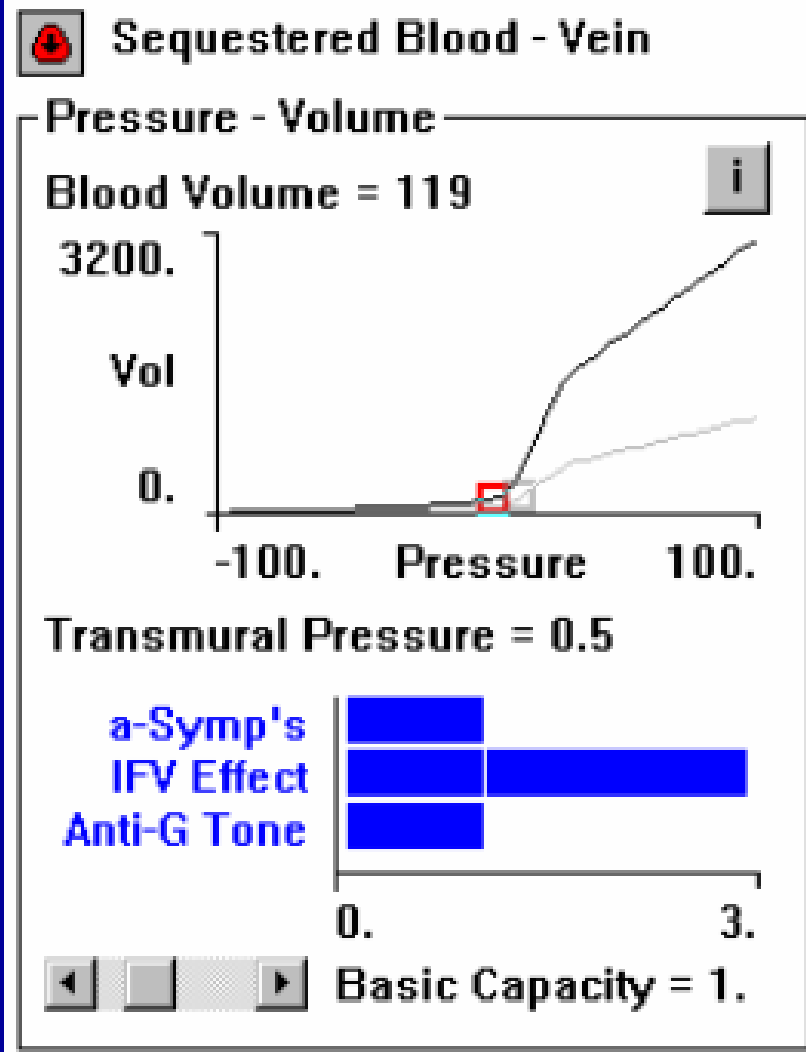


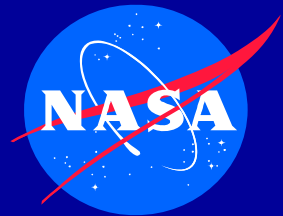
Capacitance

Preliminary Data



Model Prediction





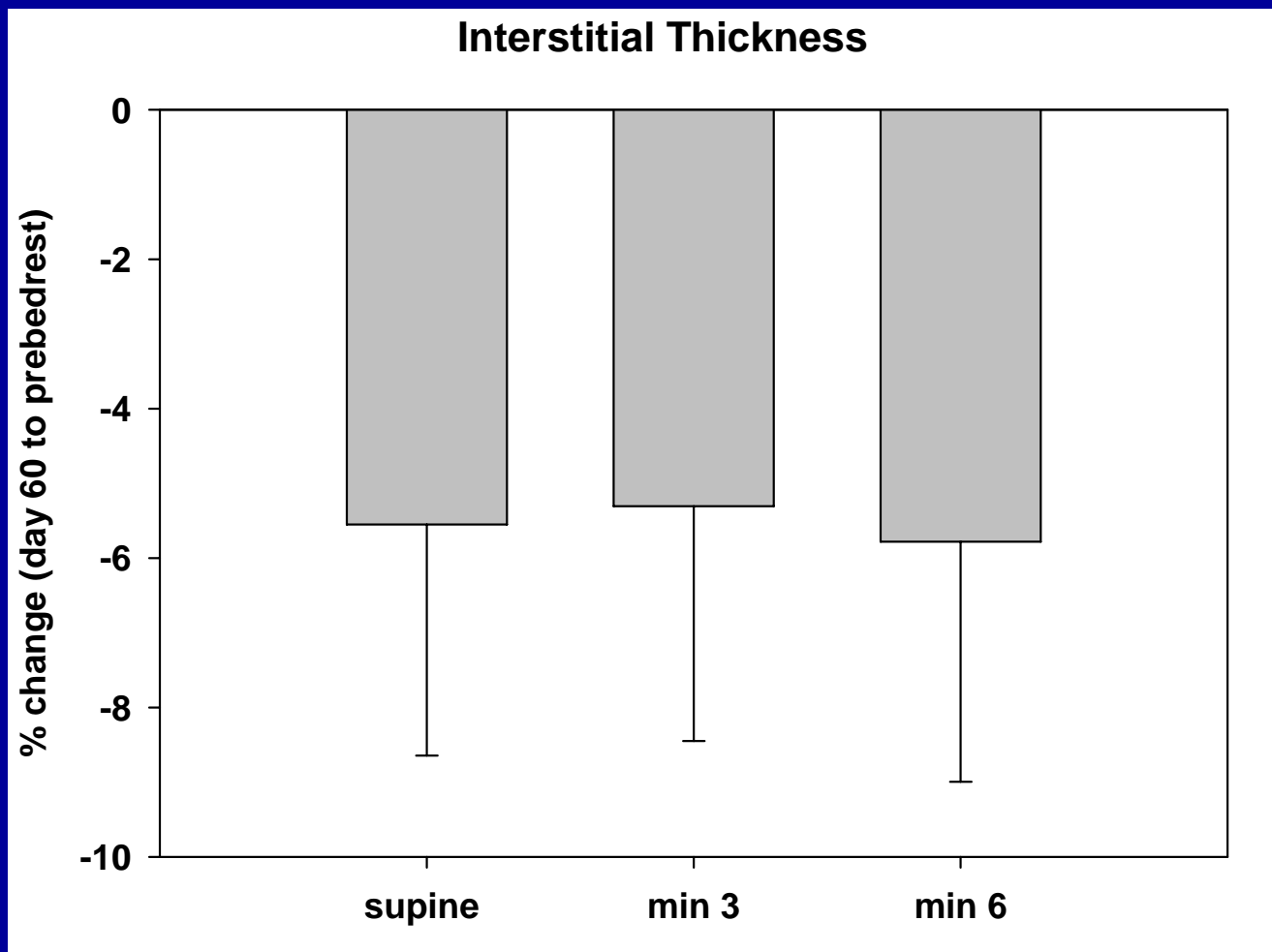
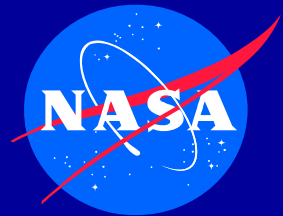
Conclusions

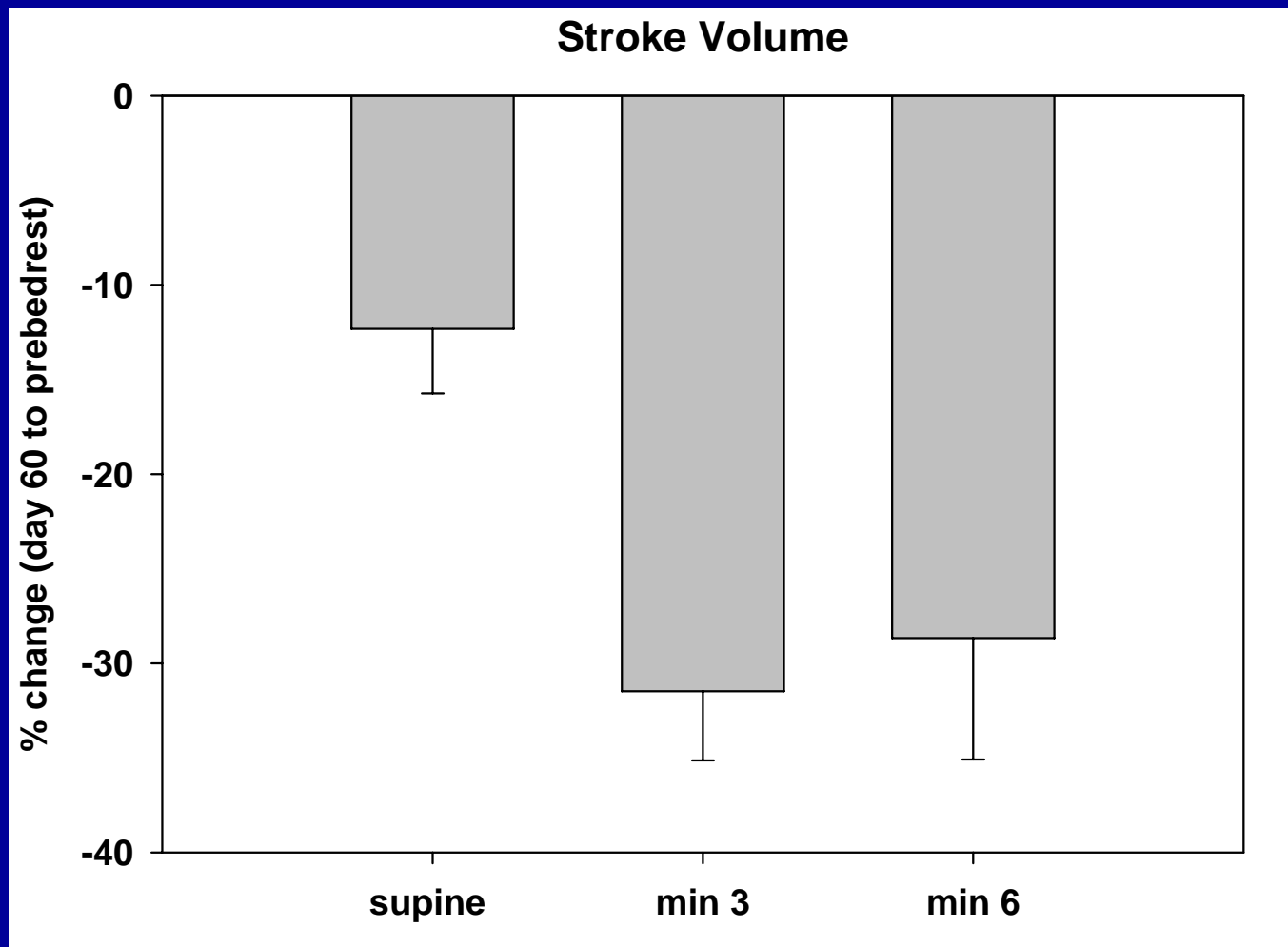
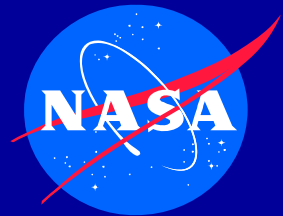
A systems analysis using a computer model of cardiovascular physiology suggests that microgravity induced interstitial volume depletion results in an accentuation of venous blood volume sequestration

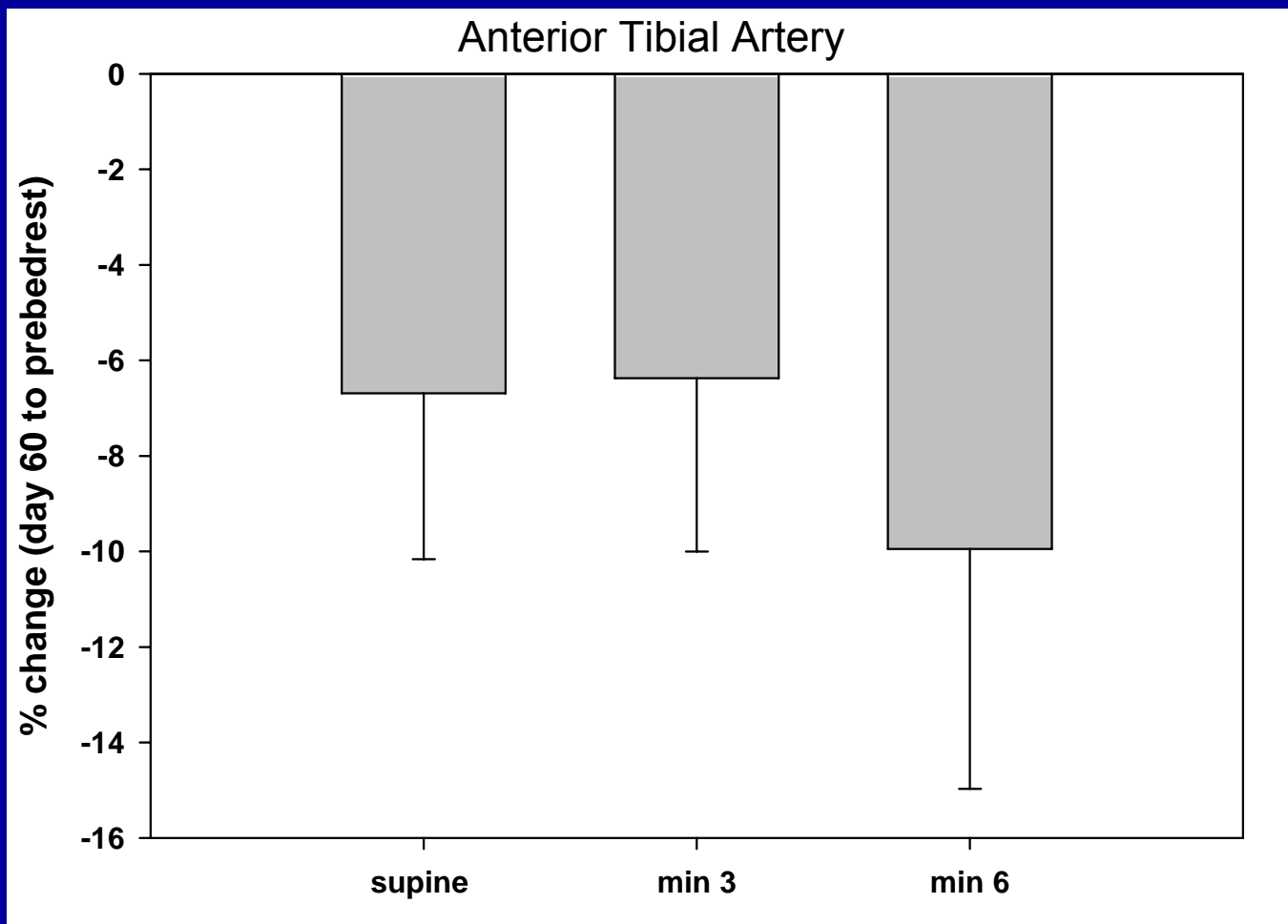
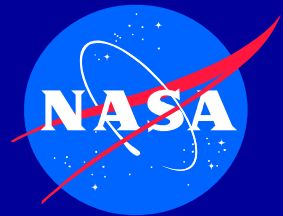
We hypothesized that long term bed rest would replicate this pattern

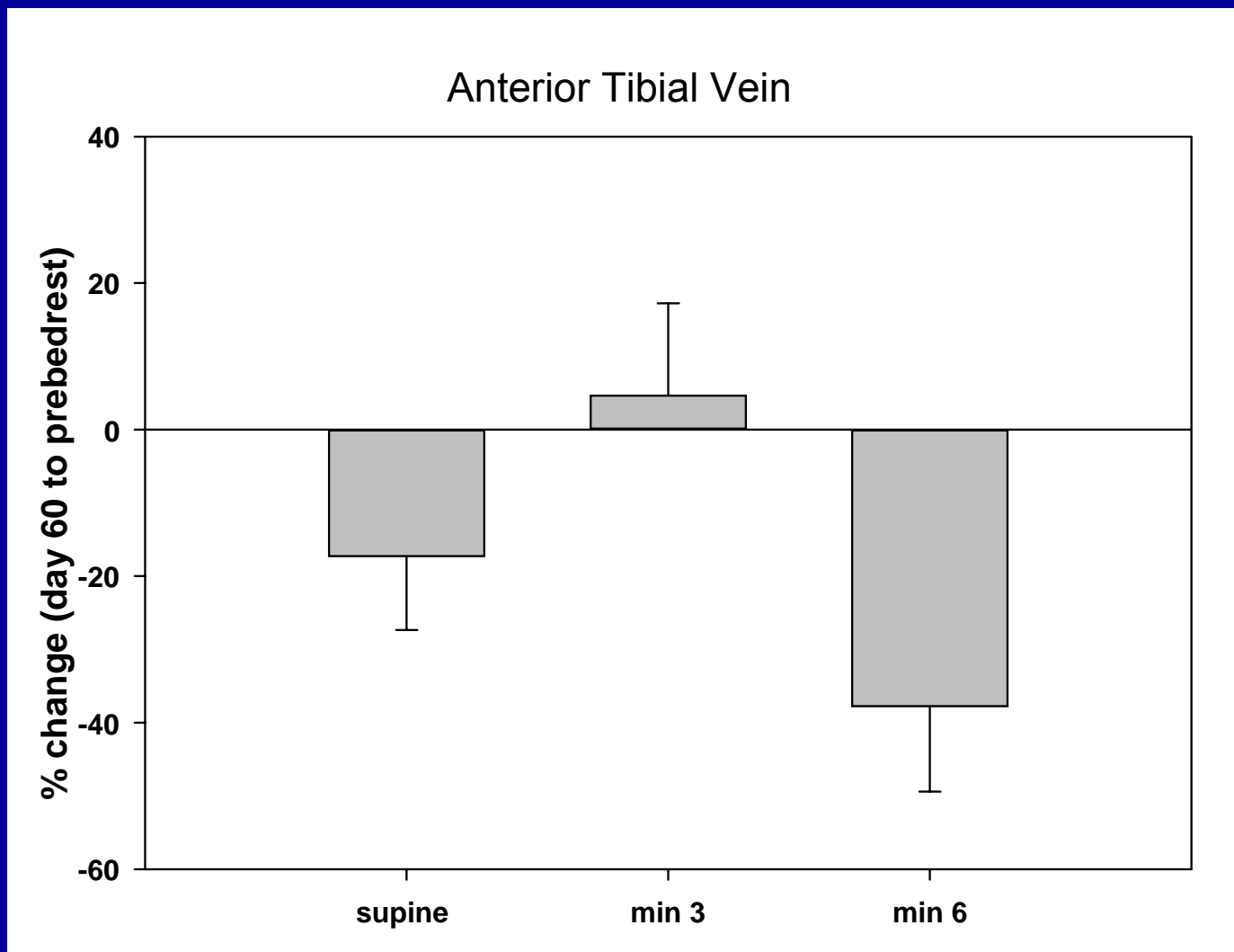
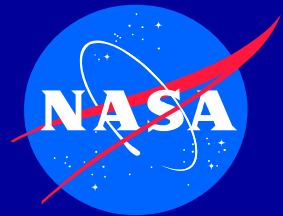
Measurements, before and after 60 days of bed rest, of changes in the interstitial spaces and observed responses of the anterior tibial vein with tilt were consistent with our hypothesis.

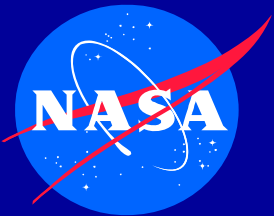
Back-up Slides



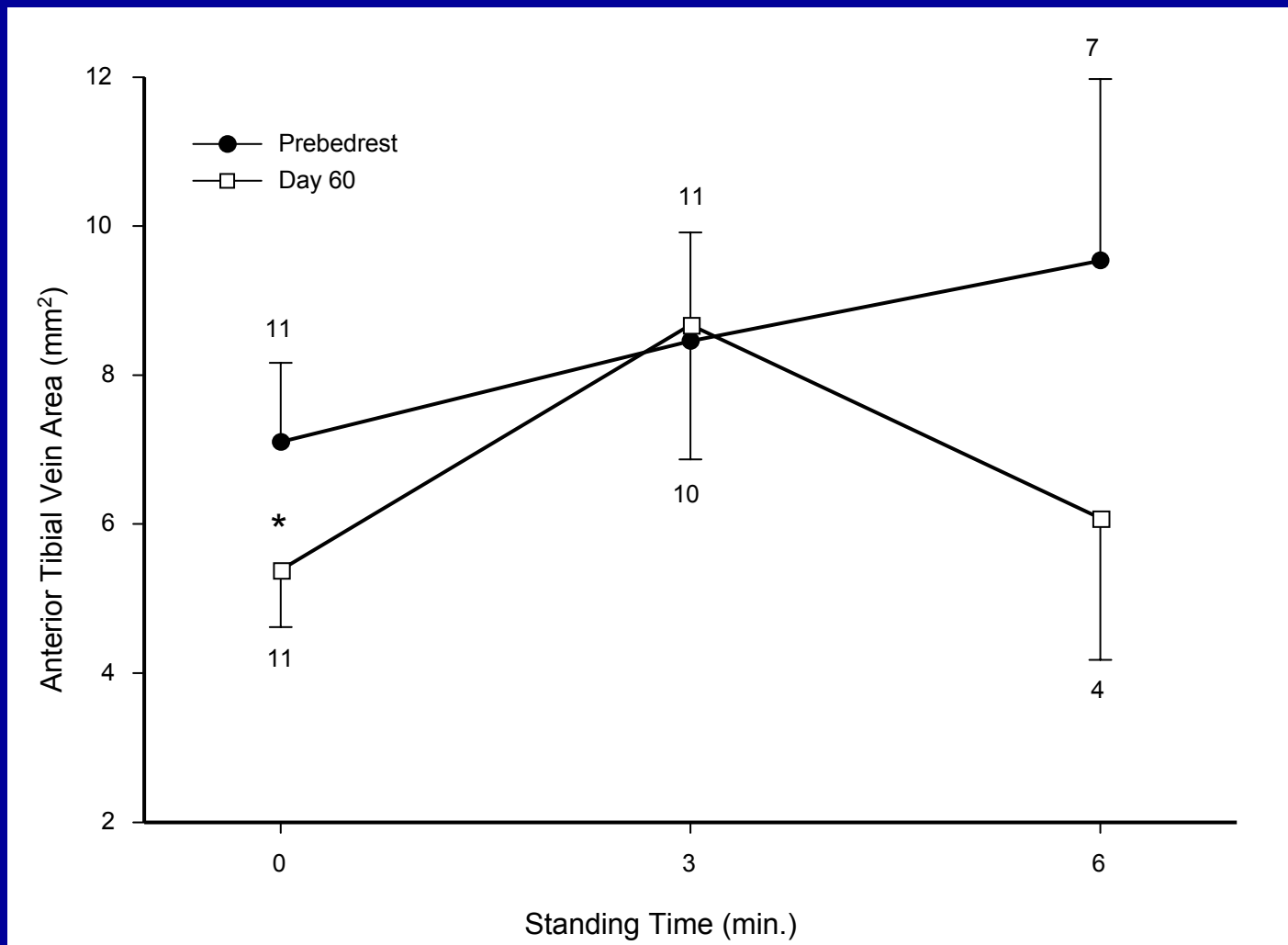


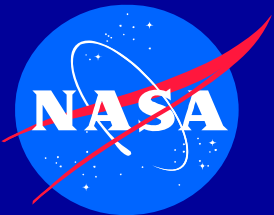






Effects of 60 Days Bed Rest on Anterior Tibial Vein Area





Tilt Test Survival Analysis Before and After 60 days of Bed Rest

